EXHIBIT 13

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF TALC

(CAS NO. 14807-96-6)

IN F344/N RATS AND B6C3F₁ MICE

(INHALATION STUDIES)

Scheduled Peer Review Date: June 23-24, 1992

NOTICE

This is a DRAFT Technical Report prepared for public review and comment. Until this DRAFT has been reviewed and approved by the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee in public session, the interpretations described herein do not represent the official scientific position of the National Toxicology Program. Following peer review, readers should contact NTP for the final version of this Technical Report.

NTP TR 421

NIH Publication No. 92-3152

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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ABSTRACT

TALC
(Non-Asbestiform)

CAS No. 14807-96-6

Molecular Formula: $Mg_3Si_4O_{10}(OH)_2$ Molecular Weight: 379.26

Synonyms: Talcum; Agalite; Emtal 596; non-asbestiform talc; non-fibrous talc; Steatite; hydrous magnesium silicate.

Talc ore may contain several other minerals including calcite, dolomite, magnesite, tremolite, anthophyllite, antigorite, quartz, pyrophyllite, micas, or chlorites. Since talc products are sold in a multitude of grades which have physical or functional characteristics especially suited for particular applications, occupational and consumer exposures to talc are complex. Recently, epidemiology studies have revealed an association between non-fibrous talc and lung cancer risk. Talc was nominated by NIOSH for study by the NTP because of widespread human exposure and because of the lack of adequate information on its chronic toxicity and potential carcinogenicity. Toxicology and carcinogenicity studies of talc (non-asbestiform, cosmetic grade), a finely powdered hydrous magnesium silicate, were conducted by exposing groups of F344/N rats to aerosols for 6 hours daily, 5 days per week for up to 113 weeks for males and 122 weeks for females. Groups of B6C3F$_1$ mice were exposed similarly for up to 103 or 104 weeks.

LIFETIME STUDY IN RATS
Groups of 50 male and 49 or 50 female rats were exposed to aerosols containing 0, 6, or 18 mg/m^3 talc until mortality in any exposure group reached 80% (113 weeks for males and 122 weeks for females). In a special study, additional groups of 22 male and 22 female rats were similarly exposed and examined for interim pathology evaluations or pulmonary function tests after 6, 11, 18, and 24 months and lung biochemistry and cytology studies after 24 months. The talc aerosols had a median mass aerodynamic diameter of 2.7 μm in the 6 mg/m^3 chamber and a median diameter of 3.2 μm in the 18 mg/m^3 chamber with geometric standard deviations of 1.9 μm. However, there was a 7-week period beginning at study week 11 during which the chamber concentration for the 18 mg/m^3 rats varied from approximately 30 to 40 mg/m^3 because of difficulties with the aerosol concentration monitoring system. Further, there was a 12-week period beginning at approximately week 70 during which there were difficulties in generating the talc aerosol, and the chamber concentrations for rats and mice were substantially lower than the target concentrations.

Survival, Body Weights, and Clinical Findings
The survival of male and female rats exposed to talc was similar to that of the controls. Mean body weights of rats exposed to 18 mg/m^3 were slightly lower than those of controls after week 65. No clinical findings were attributed to talc exposure.

Pathology Findings
Absolute and relative lung weights of male rats exposed to 18 mg/m^3 were significantly greater than those of controls at the 6-, 11-, and 18-month interim evaluations and at the end of the lifetime study, while those of female rats exposed to 18 mg/m^3 were significantly greater at the 11-, 18-, and 24-month interim evaluations and at the end of the lifetime study. Inhalation exposure of rats to talc produced a spectrum of inflammatory, reparative, and proliferative processes in the lungs. Granulomatous inflammation occurred in nearly all exposed rats and the severity increased with exposure duration and concentration. Hyperplasia of the alveolar epithelium and interstitial fibrosis occurred in or near foci of inflammation in many exposed rats, while squamous metaplasia of the alveolar epithelium and squamous cysts were also occasionally seen. Accumulations of macrophages (histiocytes), most containing talc particles, were found in the peribronchial lymphoid tissue of the lung and in the bronchial and mediastinal lymph nodes. In female rats, the incidences of alveolar/bronchiolar

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adenoma, carcinoma, and adenoma or carcinoma (combined) in the 18 mg/m³ group were significantly greater than those of controls. The incidences of pulmonary neoplasms in exposed groups of male rats were similar to those in controls.

Minor alterations attributed to talc exposure were also seen in the upper respiratory tract. Hyperplasia of the respiratory epithelium of the nasal mucosa in males and accumulation of cytoplasmic, eosinophilic droplets in the nasal mucosal epithelium in male and female rats occurred with a concentration-related increased incidence in the exposed groups.

Adrenal medulla pheochromocytomas (benign, malignant, or complex combined) occurred with a significant positive trend in male and female rats, and the incidences in the 18 mg/m³ groups were significantly greater than those of controls. Although adrenal medulla hyperplasia occurred with similar frequency among exposed and control females, the incidences of hyperplasia in exposed males were significantly lower than in controls.

Lung Talc Burden
Lung talc burdens of male and female rats exposed to 6 mg/m³ were similar and increased progressively from 6 to 24 months. Lung talc burdens of females exposed to 18 mg/m³ also increased progressively from 6 to 24 months, while those of males exposed to 18 mg/m³ remained about the same after 18 months. Lung burdens were generally proportional to exposure concentration at each interim evaluation.

Pulmonary Function, Bronchoalveolar Lavage, and Lung Biochemistry
In exposed male and female rats there was a concentration-related impairment of respiratory function which increased in severity with increasing exposure duration. The impairment was characterized by reductions in lung volume (total lung capacity, vital capacity, and forced vital capacity), lung compliance, gas exchange efficiency (carbon monoxide diffusing capacity), and nonuniform intrapulmonary gas distribution.

After 24 months, rats exposed to talc had significant increases in total protein, ß-glucuronidase, lactate dehydrogenase, alkaline phosphatase, and polymorphonuclear leukocytes in bronchoalveolar lavage fluid. Viability and phagocytic activity of macrophages recovered from lavage fluid were not affected by talc exposure.

Total lung collagen was significantly increased in rats at both exposure concentrations after 24 months, while collagenous peptides in lavage fluid and percent newly synthesized protein from females, but not males, were also significantly increased at the 6 or 18 mg/m³ levels. In addition, lung proteinase activity, primarily cathepsin D-like activity, was significantly greater in exposed males and females. Rats exposed to talc also had significant increases in collagenous peptides and acid proteinase in lung homogenates.

2-YEAR STUDY IN MICE
Groups of 47 to 49 male and 48 to 50 female mice were exposed to aerosols containing 0, 6, or 18 mg/m³ talc for up to 103 or 104 weeks. In a special study, additional groups of 39 or 40 male and 40 female mice similarly exposed were examined for interim pathology evaluations, lung biochemistry, and cytology studies after 6, 12, and 18 months of exposure. The talc aerosols had a median mass aerodynamic diameter of 3.3 μm with a geometric standard deviation of 1.9 μm in the 6 mg/m³ chamber, and a median diameter of 3.6 μm with a geometric standard deviation of 2.0 μm in the 18 mg/m³ chamber.

Survival, Body Weights, and Clinical Findings
Final mean body weights and survival of male and female mice exposed to talc were similar to those of the controls. There were no clinical findings attributed to talc exposure.

Pathology Findings
Inhalation exposure of mice to talc was associated with chronic active inflammation and the accumulation of macrophages in the lung. In contrast to rats, hyperplasia of the alveolar epithelium, squamous metaplasia, or interstitial fibrosis were not associated with the inflammatory response in mice, and the incidences of pulmonary neoplasms in exposed and control groups of mice were similar. Accumulations of macrophages (histiocytes) containing talc particles were also present in the bronchial lymph node.

In the upper respiratory tract, cytoplasmic alteration, consisting of the accumulation of cytoplasmic eosinophilic droplets in the nasal mucosal epithelium, occurred with a concentration-related increased incidence in exposed male and female mice.

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Lung Talc Burden

Lung talc burdens of mice exposed to 6 mg/m³ were similar between males and females and increased progressively from 6 to 24 months, except for males at 18 months. The lung talc burdens of mice exposed to 18 mg/m³ were also similar between the sexes at each interim evaluation. Although the talc burdens of males and females increased substantially from 6 to 24 months, the values at 12 and 18 months were similar. Generally, lung burdens of mice exposed to 18 mg/m³ were disproportionately greater than those of mice exposed to 6 mg/m³, suggesting that clearance of talc from the lung was impaired, or impaired to a greater extent, in mice exposed to 18 mg/m³ than in mice exposed to 6 mg/m³.

Bronchoalveolar Lavage and Lung Biochemistry

Increases in total protein, ß-glucuronidase, lactate dehydrogenase, and glutathione reductase, total nucleated cells, and polymorphonuclear leukocytes in bronchoalveolar lavage fluid were observed primarily in mice exposed to 18 mg/m³, although some parameters were also increased in mice exposed to 6 mg/m³.

The amount of collagenous peptides in lavage fluid and total lung collagen were increased in male and female mice exposed to 18 mg/m³. Acid proteinase activity, principally cathepsin D-like activity, of lung homogenate supernatant fluid was also significantly increased in mice at the 18 mg/m³ exposure concentration.

CONCLUSIONS

Under the conditions of these inhalation studies, there was *some evidence of carcinogenic activity** of talc in male F344/N rats based on an increased incidence of benign and malignant pheochromocytomas of the adrenal gland. There was *clear evidence of carcinogenic activity* of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign and malignant pheochromocytomas of the adrenal gland. There was *no evidence of carcinogenic activity* of talc in male or female B6C3F₁ mice exposed to 6 or 18 mg/m³.

The principal toxic lesions associated with inhalation exposure to talc in rats included chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous metaplasia and squamous cysts, and interstitial fibrosis of the lung. These lesions were accompanied by impaired pulmonary function characterized primarily by reduced lung volumes, reduced dynamic and/or quasistatic lung compliance, reduced gas exchange efficiency, and nonuniform intrapulmonary gas distribution. In mice, inhalation exposure to talc produced chronic inflammation of the lung with the accumulation of alveolar macrophages.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.

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Summary of the Lifetime and 2-Year Carcinogenicity Studies of Talc

	Male F344/N Rats	Female F344/N Rats	Male B6C3F₁ Mice	Female B6C3F₁ Mice
Exposure levels	0, 6, or 18 mg/m³	0, 6, or 18 mg/m³	0, 6, or 18 mg/m³	0, 6, or 18 mg/m³
Body weights	High-dose group slightly lower than controls	High-dose group slightly lower than controls	Exposed groups similar to controls	Exposed groups similar to controls
Survival rates	9/50, 14/50, 16/50	11/50, 13/49, 9/50	30/47, 28/48, 32/49	30/49, 23/48, 25/50
Neoplastic effects	Adrenal medulla: benign or malignant pheochromocytoma (26/49, 32/48, 37/47)	Lung: alveolar/bronchiolar adenoma (1/50, 0/48, 9/50); alveolar/bronchiolar carcinoma (0/50, 0/48, 5/50); alveolar/bronchiolar adenoma or carcinoma (1/50, 0/48, 13/50) Adrenal medulla: benign or malignant pheochromocytoma (13/48, 14/47, 23/49)	None	None
Nonneoplastic effects	Lung: granulomatous inflammation (2/49, 50/50, 49/50); interstitial fibrosis (1/49, 16/50, 33/50); alveolar epithelial hyperplasia (5/49, 26/50, 38/50); peribronchial hyperplasia (0/49, 12/50, 8/50); cyst (0/49, 0/50, 3/50); alveolar squamous metaplasia (0/49, 0/50, 2/50) Lymph node (bronchial): histiocytic hyperplasia (0/41, 44/48, 46/49); (mediastinal) histiocytic hyperplasia (0/48, 40/49, 43/47) Nose: respiratory epithelial hyperplasia (0/49, 3/48, 14/47); cytoplasmic alteration (3/49, 18/48, 40/47)	Lung: granulomatous inflammation (2/50, 47/48, 50/50); interstitial fibrosis (1/50, 24/48, 44/50); alveolar epithelial hyperplasia (2/50, 27/48, 47/50); peribronchial hyperplasia (0/50, 8/48, 9/50); cyst (0/50, 1/48, 7/50); alveolar squamous metaplasia (0/50, 0/48, 8/50) Lymph node (bronchial): histiocytic hyperplasia (0/46, 40/47, 45/47); (mediastinal) histiocytic hyperplasia (0/47, 33/44, 40/47) Nose: cytoplasmic alteration (5/48, 23/45, 46/48)	Lung: chronic inflammation (0/45, 16/47, 40/48); macrophage hyperplasia (3/45, 46/47, 48/48) Lymph node (bronchial): histiocytic hyperplasia (1/32, 32/39, 42/44) Nose: cytoplasmic alteration (5/45, 23/46, 40/47)	Lung: chronic inflammation (0/46, 25/48, 38/50); macrophage hyperplasia (2/46, 45/48, 43/50) Lymph node (bronchial): histiocytic hyperplasia (0/38, 25/37, 39/43) Nose: cytoplasmic alteration (29/46, 37/46, 40/50)
Level of evidence of carcinogenic activity	Some evidence	Clear evidence	No evidence	No evidence

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EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (clear evidence and some evidence); one category for uncertain findings (equivocal evidence); one category for no observable effects (no evidence); and one category for experiments that cannot be evaluated because of major flaws (inadequate study). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

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NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on talc on June 23-24, 1992, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

NOTE: A summary of the Technical Reports Review Subcommittee's remarks will appear in a future draft of this report.

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INTRODUCTION

TALC
(Non-Asbestiform)

CAS No. 14807-96-6

Molecular Formula: $Mg_3Si_4O_{10}(OH)_2$ Molecular Weight: 379.26

Synonyms: Talcum; Agalite; Emtal 596; non-asbestiform talc; non-fibrous talc; Steatite; hydrous magnesium silicate

CHEMICAL AND PHYSICAL PROPERTIES

Talc is a fine powder, white to grayish white in color, with a greasy feel and luster. It is insoluble in water, cold acids, and alkalies (*Merck Index,* 1983), has a density of 2.7 to 2.8, and a melting point of 900° to 1,000° C (Hawley, 1977). Talc as a pure mineral is composed of 63.5% SiO_2, 31.7% MgO, and 4.8% H_2O (Pooley and Rowlands, 1977).

PRODUCTION, USE, AND HUMAN EXPOSURE

Talc is produced by open pit or underground mining of talc rocks and processed by crushing, drying, and milling. Contaminating minerals including iron, nickel, manganese, chromium, aluminum, and titanium are separated from talc by flotation or elutriation. Talc is then finely powdered, treated with boiling diluted hydrochloric acid, washed well, and dried (Osol, 1980). Geological formation of talc rock results from the alteration of magnesia- and silica-rich ultramafic rocks under a range of temperatures and pressures. These hydrothermal alterations may lead to the formation of other mineral phases such as tremolite and serpentine minerals, including chrysotile. These mineral phases may occur as microscopic intergrowths, nodules, or discrete zones within or adjacent to talc (Rohl *et al.,* 1976).

United States production of talc for 1985 was estimated at 1.1 million metric tons, with industrial pattern of use as follows: ceramics, 37%; paints, 19%; paper, 10%; roofing, 10%; plastics, 7%, cosmetics, 5%; rubber, 3%; insecticides, 1%; and other uses, 9% (Bureau of Mines, 1986). Commercial talc is categorized into cosmetic grade, which is free of asbestos, and industrial grade, which contains other minerals including asbestos (Hildick-Smith, 1976).

A comprehensive review of the literature before 1987 on the use, exposure, and biological effects of talc was published by IARC (1987). Talc is used as a dusting powder, including baby powder, either alone or with starch or boric acid, for medicinal or toiletry preparations; as an excipient and filler for pills and tablets; and for dusting tablet molds (*Merck Index,* 1983). It is also used as a filler and pigment for paints, putty, and plaster; as a carrier and diluent for pesticides; as an additive to clay in ceramic manufacture; in paper coatings; and for the manufacture of rubber and roofing materials (Hawley, 1977). The recommended time-weighted average (TWA) human exposure level for talc containing no asbestos fibers is 2 mg/m^3 (ACGIH, 1989).

A large segment of the population is potentially exposed to talc. The number of workers exposed to talc was estimated at 1,371,201, which includes 349,228 females (NIOSH, 1990). In addition, the public is potentially exposed to talc through its many uses in pharmaceuticals and consumer products. Based on its uses, human exposure to talc can occur via inhalation, ingestion, or dermal exposure.

ABSORPTION, DISTRIBUTION, AND EXCRETION

Experimental Animals

The absorption and disposition of ³H-labeled talc in rats, mice, and guinea pigs administered a single oral dose, as well as its translocation in rabbits administered a single or multiple intravaginal dose was studied by Phillips *et al.* (1978). The oral doses

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were 50 mg/kg for rats, 40 mg/kg for mice, and 25 mg/kg for guinea pigs. Rabbits were given either a single intravaginal dose of 50 mg/kg or the same dose once a day for 6 days. In rats, mice, and guinea pigs, more than 95% of the dose was excreted in the feces 3 to 4 days after dosing. Less than 2% of the radioactivity was recovered in the urine. This radioactivity probably reflected contamination of urine samples with feces. No radioactivity was found in the liver or kidneys of these animals. No translocation of talc was found in the ovaries of rabbits.

Hanson *et al* (1985) and Pickrell *et al* (1989) studied the lung burden in groups of 5 male and 5 female F344/N rats and B6C3F$_1$ mice following inhalation exposure to concentrations of talc for 6 hours daily, 5 days per week, for 4 weeks. The mean exposure concentrations used were 2.3, 4.3, or 17 mg/m^3 for rats and 2.2, 5.7, or 20.6 mg/m^3 for mice. The resulting lung talc burdens were 0.08, 0.19, and 0.87 mg/g of lung for rats and 0.1, 0.33, and 1.2 mg/g of lung for mice. These data clearly indicate that the amount of talc retained per unit of lung tissue was proportional to the exposure concentration of talc.

Pulmonary deposition, translocation, and clearance of neutron-activated talc was studied in hamsters after a single, 2-hour, nose-only inhalation exposure (Wehner *et al*, 1977a,b). Deposition of talc in the lung was demonstrated by X-ray fluorescence and X-ray diffraction. An estimated 6% to 8% of the inhaled quantity was deposited in the alveoli. The biological half-life of the talc deposited in the alveoli was estimated at 7 to 10 days. No translocation of talc to liver, kidneys, ovaries, or other parts of the body was found.

Humans

Talc, a filler in some drugs injected by addicts, was found in the lung (Groth *et al*, 1972; Lamb and Roberts, 1972; Farber *et al*, 1981; Crouch and Churg, 1983), spleen, kidney, liver, brain, adrenal gland, thyroid gland (Groth *et al*, 1972), and retina (Atlee, 1972) of some addicts. In the lung, most of the talc particles were seen within the vessels of the alveolar walls and were often associated with marked foreign body granulomas (Crouch and Churg, 1983).

Toxicity

Experimental Animals

The LD$_{50}$ for talc has not been established. Talc caused death in guinea pigs given 2 or 3 injections of 25 mg talc in saline (Dogra *et al*, 1977) and in rats receiving a splenic injection of 1,400 mg/kg body weight (Eger and DaCanalis, 1964). Deaths occurred in rats exposed to a very dense atmosphere of talc (particle size <5 μm) 3 hours a day, for 12 days (Policard, 1940). The concentration of talc in the atmosphere was not known and the observed mortality may have been due to suffocation.

Wagner *et al* (1977) reported on the toxic effects of talc in rats exposed orally or by inhalation. No significant decrease in mean life span and no pathologic effects were found in rats fed 100 mg talc for 101 days. Rats exposed to talc atmospheres of 10.8 mg/m^3 (particle size, 25 mm) for 3 months showed minimal lung fibrosis, and no change in severity occurred during the postexposure period. By contrast, rats exposed to the same atmospheres for 1 year showed minimal to slight fibrosis, and the severity had increased to moderate within a year after cessation of exposure. Rats exposed to atmospheres of 30 to 383 mg/m^3 "industrial" or "pharmaceutical" talc for 9 months developed chronic inflammatory changes, including thickening of the pulmonary artery walls and emphysema (Bethege-Iwanska, 1971). Hamsters exposed to respirable aerosols containing 8 mg/m^3 of cosmetic grade talc for 150 minutes a day, 5 days per week, for 300 days showed no histopathologic changes in the lung, heart, liver, renal tissue, or uterus (Wehner, 1980).

Rats given a single intratracheal injection of 50 mg of pure talc in water did not show lung fibrosis or lymph node abnormalities. Those given the same dose of "calcined" talc developed lung and lymph node fibrosis (Luchtrath and Schmidt, 1959). These differing results may be related to differences in the crystal structures of "pure" and "calcined" talc. Bronchiolar inflammation occurred in rats 4 days after an intratracheal injection of 25 mg of talc (containing tremolite) in water; collagenous tissue developed within a few months after injection (Gross *et al*, 1970).

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Injection of 10 mg of talc containing some asbestos into the pleural cavity of mice produced granulomas (Davis, 1972). A single injection of 20 mg of talc into the right pleural cavity of rats produced granulomas at the injection site; one lung adenoma was also observed but no other changes related to talc administration were observed in the lung (Wagner et al., 1977). Rats with abdominal muscle implants of suture materials dusted with talc or talc pellets initially showed mild to moderate acute inflammation, followed by chronic inflammation and granuloma formation within 3 days (Sheikh et al., 1984).

Rats with subcutaneous inflammation caused by talc had a decrease in bone formation as evidenced by hypozincemia and a decrease in metaphyseal trabecular surfaces. Both hypozincemia and the decrease in osteoblast trabecular surfaces were directly proportional to the number of granulomas present (Marusic et al., 1990).

Talc produced retinopathy in adult Rhesus monkeys given intravenous injections of talc once every 2 weeks for 3.5 to 10 months. Talc particles were found lodged in the precapillary arterioles and capillaries, producing a focal occlusion of retinal and choroidal capillaries (Kaga et al., 1982a,b).

Humans

Exposure to industrial grade talc dust causes pulmonary fibrosis, however, reports on cosmetic grade talc dust are conflicting. Hildick-Smith (1976) reported that cosmetic grade talc did not appear to be injurious to health, while Vallyathan and Craighead (1981) reported that it was. Four of seven workers exposed to heavy concentrations (0.4 to 36 mg/m^3) of cosmetic grade talc for 4 to 27 years had histologic evidence of pulmonary fibrosis at death (Thariault et al., 1974). Wells et al. (1979) also noted chronic pulmonary degenerative disease in a housewife who reported heavy use of cosmetic talc. Inhalation of pure talc is known to result in a disease known as talcosis, which may include acute or chronic bronchitis and interstitial inflammation. Radiographically, the lesion appears as a small, irregular nodule, typical of a small-airway obstruction. Intravenous administration of talc-containing oral medications by abusers causes vascular granulomas (Feigin, 1986). Intravenous talcosis was diagnosed in a 36-year-old woman who was a drug abuser (Hill et al., 1990). Talcosis in this patient was identified by the presence of peripheral nodular lesions on chest X-rays and was confirmed by the presence of birefringent particles

in a transbronchial biopsy. Pulmonary talc granulomatosis was diagnosed in a cocaine sniffer (Oubeid et al., 1990). Chest X-rays of a heroin addict who later died of respiratory failure showed a progressive massive fibrosis of the lung secondary to intravenous injection of the drug (Crouch and Churg, 1983). Microscopic examination of lung lesions revealed an active granulomatous reaction with associated vascular obliteration. Throughout the lesion, refractile birefringent plates of particulate material were noted. Interstitial perivascular and vascular granulomas were noted in the periphery of the lung. The particulate material was identified as talc by X-ray spectroscopy and diffraction methods. Intravenous injection of talc-containing drugs intended for oral use was the cause of pulmonary granulomatosis and pulmonary hypertension in 19 patients (Arnett et al., 1976). In patients with pulmonary hypertension, talc granuloma was found in the pulmonary arteries. In patients without hypertension, talc granuloma was found in the pulmonary interstitium. Patients suffering from talc granulomatosis (confirmed by lung biopsy) as a result of intravenous injection of crushed tablets of pentazocine, had dyspnea, increased angiotensin-converting enzyme concentrations, and increased lymphocytes by bronchoalveolar lavage (Farber et al., 1982). Pneumoconiosis (talcosilicosis) was diagnosed in a 54-year-old female confectionery worker who was exposed to talc dust for 5 years (Canessa et al., 1990). Talc, given by intrapleural instillation to promote pleural symphysis in the palliation of recurrent malignant pleural effusions, caused adult respiratory distress syndrome (ARDS) in three patients (Rinaldo et al., 1983). Symptoms of ARDS included fever, dyspnea, and respiratory failure. ARDS occurred in a 16-month-old baby inhaling baby powder. Normal pulmonary function returned in this patient after 6 years, as determined by a follow-up study (Reyes and Brown, 1989).

CARCINOGENICITY

Experimental Animals

Results of carcinogenicity studies of talc in animals were reviewed by the IARC (1987). The following is an excerpt of this review:

No significant difference in tumor incidence was observed between two groups of Wistar rats (25 animals/sex/group, 10 weeks old) given an equivalent of 50 mg/kg per day of commercial talc (composition not specified) in the diet or the basal diet for life (Gibel et al., 1976). Similar results were obtained in groups of 16 male and 16 female

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Wistar rats (21 to 26 weeks old) given 100 mg of Italian talc (particle size, 25 mm; containing 92% talc, 3% chlorite, 1% carbonate minerals, and 0.5 to 1% quartz) per rat per day in the diet or the basal diet for 5 months and observed for life (Wagner *et al*, 1977). In both studies small numbers of animals were used.

Groups of 24 male and female Wistar rats, 6 to 8 weeks of age, were exposed by inhalation to 10.8 mg/m^3 Italian talc aerosol 7.5 hours a day, 5 days per week, for 6 or 12 months. Ten days after the end of each exposure period, 6 rats in each group were killed; an additional 4 rats were killed one year later. Within 28 months from the beginning of the study, 12 animals in each group had died. No lung tumors were observed in rats exposed to talc for 6 months; one lung adenoma occurred among rats exposed for 12 months. No lung tumors were found in the control rats (Wagner *et al*, 1977). The adequacy of this study is in question because only a small number of rats survived longer than 12 months.

Three groups of 50 male and female hamsters, 4 weeks of age were exposed to talc aerosol (37.1 mg/m^3, mean respirable fraction 9.8 mg/m^3) for 3, 30, or 150 minutes per day, 5 days a week, for 30 days. Two additional groups of hamsters were exposed to talc aerosol (27.4 mg/m^3, mean respirable fraction 8.11 mg/m^3) for 30 or 150 minutes per day, for 300 days. Two groups of 25 male and female hamsters were exposed to air and served as controls. No primary tumors were found in the respiratory system of any hamster. Twenty-five percent of the hamsters exposed to the aerosols for 30 or 150 minutes for 300 days had alveolar cell hyperplasia compared to 10% in the controls (Wehner *et al*, 1977a, 1979). The exposure duration of this study was short and considered inadequate.

No local tumors were found in 50 female R3 mice, 3 to 6 months of age, given a 0.2 mL subcutaneous injection of talc of unspecified composition (80 mg talc in peanut oil) and observed for life (Neukomm and de Trey, 1961).

Forty Swiss albino rats, 6 weeks of age and sex unspecified, received a single intraperitoneal injection of 20 mg commercial talc (unspecified composition) in saline. Sixteen animals died by the end of 6 months. Of the 24 mice that lived to termination (time not specified) three had peritoneal mesotheliomas compared to 3 of 46 of the controls

(Ozesmi *et al*, 1985). This study was considered inadequate because of poor reporting.

Forty female Wistar rats, 8 to 12 weeks of age, were given four intraperitoneal injections of 25 mg granular talc in 2 mL saline at weekly intervals. Similarly, 80 females were injected with saline and served as controls. The rats were observed until termination or death (average survival time, 602 days). A mesothelioma occurred in 1 of 36 rats given talc but none was found in the controls (Pott *et al*, 1974, 1976a,b).

No mesothelioma was observed in two groups of 24 male and female Wistar rats given a single intrapleural injection of 20 mg Italian talc in saline or saline alone. A pulmonary adenoma occurred in one rat that died at 25 months. Mean survival time (655 days for the talc group versus 691 for the controls) was not affected (Wagner *et al*, 1977).

Groups of 30 to 50 female Osborne-Mendel rats, 12 to 20 weeks of age, received intrapleural implantation of one of seven grades of refined commercial talc from separate sources in hardened gelatin. Rats were observed for up to 2 years at which time survivors were killed. Pleural sarcoma incidences were: grade 1, 1/26; grade 2, 1/30; grade 3, 1/29; grade 4, 1/29; grade 5, 0/30; grade 6, 0/30; grade 7, 0/29. The incidence of pleural sarcoma was 3 of 491 in untreated controls, 17 of 615 in controls receiving implants of "nonfibrous" material described by the authors as "noncarcinogenic," and 14 of 29 in rats receiving UICC crocidolite asbestos (Stanton *et al*, 1981).

The IARC Working Group noted that in most of the talc studies, no or limited characterization of the mineralogy, fiber content, or particle size of the samples was given. Thus, the group concluded that there was inadequate evidence on the carcinogenicity of talc to experimental animals.

Humans

An epidemiological study of pottery workers in the United States revealed an association between exposure to non-fibrous talc and increased mortality and lung cancer incidence (Thomas and Stewart, 1987). Increased incidences of lung cancer occurred exclusively among pottery workers employed in the manufacture of plumbing fixtures. A later study of employees in three ceramic plumbing fixture factories showed increased mortality from benign respiratory disease and from lung cancer. The

increased incidence in lung cancer was highest among workers who were simultaneously exposed to silica and talc. The lung cancer mortality risk increased with the number of years of exposure to talc, but showed no pattern by the number of years of exposure to silica. Among men exposed to talc, lung cancer risk decreased with age at first exposure to non-fibrous talc and increased with years since first exposure (Thomas, 1990). Whether or not exposure to silica had a promoting effect on lung cancer is not known. No increased risk for lung cancer or benign respiratory disease was found among miners of non-asbestiform talc or talc millers (Wergeland et al., 1990).

A case-control study showed that women who had perineal exposure to deodorizing powders alone or in combination with other talc-containing powders, had a 2.8 times higher risk of developing borderline ovarian tumors than women who were not perineally exposed to powder (Harlow and Weiss, 1989). In an earlier study, the use of talc as a dusting powder on the perineum or on sanitary napkins by women was associated with an increased risk of epithelial ovarian cancer. Women engaged in both practices had a relatively higher risk of developing this type of cancer (Cramer et al., 1982). No information was presented regarding exposure levels or the content of contaminating minerals of the talc used. In another study, the role of exposure to talcum powder, tobacco, alcohol, and coffee, and the histories of tubal sterilization and hysterectomy on ovarian cancer risk was assessed. The study involved 188 women diagnosed with epithelial ovarian cancer and 539 control women. No association was found between the incidence of epithelial ovarian cancer and increasing frequency or duration of talc use, and patients did not differ from control women in the use of talc on sanitary pads, contraceptive diaphragms, or both. (Whittemore et al., 1988).

REPRODUCTIVE AND TERATOGENIC EFFECTS

Experimental Animals
Talc produced nonspecific abnormalities in chicken eggs at incidences similar to those caused by thalidomide and sulphadimethoxine (Yang, 1977).

No teratologic effects were observed in hamsters, rats, mice, or rabbits after oral administration of talc. The doses used were 1,600 mg/kg for rats and mice on days 6 through 15 of gestation, 1,200 mg/kg for hamsters on days 6 through 10 of gestation, and 900 mg/kg for rabbits on days 6 through 18 of gestation (Food and Drug Research Laboratories, 1973).

Humans
No information on the reproductive or teratogenic effects of talc in humans has been reported.

GENETIC TOXICOLOGY
There are no published studies on the genotoxicity of talc. The IARC (1987) review of talc included unpublished results from a 1974 study conducted by Litton Bionetics that showed no mutagenic activity for talc in vitro or in vivo. Talc did not induce mutations in Salmonella typhimurium strains TA1530 or HisG46, or in the yeast, Saccharomyces cerevisiae. No chromosomal aberrations were observed in human fibroblasts treated with talc in vitro. In vivo tests conducted in rats gave negative results for induction of chromosomal aberrations in bone marrow cells and dominant lethal mutations in germinal cells.

STUDY RATIONALE
Talc was nominated by NIOSH in 1978 for testing by NTP because of the paucity of adequate information on its carcinogenicity and because of widespread human exposure. The inhalation route was chosen because it is the most common route for human exposure.

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